Krystal

The Leader in Redosable Gene Therapy for Rare Disease

April 2021

Forward-looking statements

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Krystal overview

A fully integrated, clinical stage gene therapy company powered by proprietary HSV-1 vector technology

Differentiated viral vector platform enables *in vivo*, repeat dose gene therapies

- Proprietary, engineered *replication incompetent* HSV-1 based platform
- Clinical data shows maintenance of safety and transgene expression after repeat dosing
- Positive external clinical and regulatory precedent with *in vivo* HSV-1 based therapy

Initial focus on rare, dermatologic indications led to rapid clinical proof of concept and pipeline

- Lead program, B-VEC (formerly KB103) went from IND to Phase 3 in less than 3 years; pivotal data anticipated in 4Q21
- Two lead dermatologic pipeline programs, KB104 and KB105, leverage the same vector

Broadening focus to address larger indications and new tissue types

- Ongoing Phase 1 trial in acne scars and wrinkles with KB301, under our wholly owned subsidiary Jeune, Inc.
- Positive pre-clinical data from KB407 for cystic fibrosis demonstrates potential to target lung tissue; pre-IND studies underway
- Continue to drive innovation by investing in next-gen platform capabilities

In-house GMP manufacturing to support clinical and commercial needs

- Stable producer cell lines developed for each program have cost, scale, and regulatory benefits
- Current ~7,500 sqft GMP facility near company headquarters in Pittsburgh is producing pivotal material at commercial scale, and BLA readiness is underway
- Investing in additional capacity via construction of an ~150,000 sqft facility which is expected to be operational in 2022

Upcoming Milestones

Progress across pipeline will yield pivotal data for B-VEC, a 4th clinical stage program and a new respiratory candidate in 2021

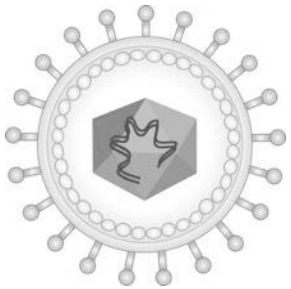
	Timing	Program	Event
☑	1Q21	B-VEC for DEB	Complete enrollment in pivotal GEM-3 study in DEB
☑	1Q21	KB301 for aesthetic indications	Announce Initial safety data from cohort 1 of Phase 1 study in facial wrinkles and acne scars
☑	1Q21	KB301 for aesthetic indications	Provide update on strategy for KB301 and aesthetic pipeline (under Jeune Inc.)
	1H21	KB105 for TGM1-ARCI	Announce initial Phase 2 data and update on next Phase 2 cohorts
☑	1H21	KB407 for CF	Announce data from IND enabling toxicology study in nonhuman primates
☑	1H21	Respiratory pipeline	Announce development candidate for new genetic lung disease
	1H21	B-VEC	Present detailed Phase 1/2 safety summary at SID (May 3-8)
	1H21	KB301	Present detailed Phase 1 (cohort 1) safety summary at SID (May 3-8)
	3Q21	KB407 for CF	Initiate Phase 1/2 study
	2H21	KB104 for Netherton	File IND
	2H21	KB301 for aesthetic indications	Initial efficacy data from Phase 1 study
	4Q21	**B-VEC for DEB**	**Announce top line data from the pivotal GEM-3 study**

All pipeline compounds are investigational, being evaluated in clinical or pre-clinical studies.

Our technology platform enables noninvasive, redosable gene therapy

HSV-1 is positively differentiated vs. other gene therapy technologies

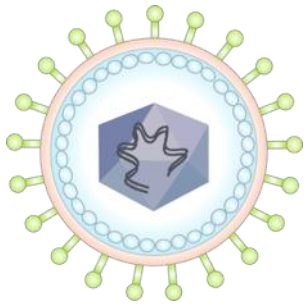
Wild-type HSV-1



HSV-1 has natural affinity for epithelial cells (in addition to several other cell types) with favorable immune-evasion mechanisms

Targeted mutagenesis resulting in platform that is both safe and effective for localized, repeat delivery of genetic payload

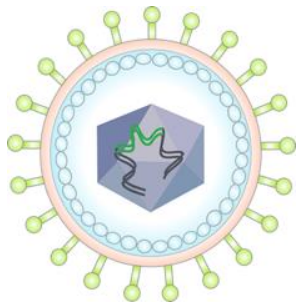
Krystal's Modified HSV-1 Platform



Replication incompetent HSV-1 vector that can be administered repeatedly for chronic dosing

Insertion of one or more therapeutic effectors of interest into the vector

Therapeutic Vector



Large carrying capacity allows insertion of large transgenes, multiple copies of the transgene of interest and/or multiple different transgenes

Vector Platform Comparison

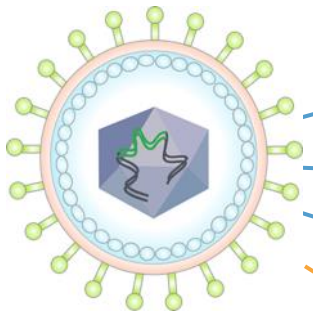
	LV	AAV	HSV-1	LNP
In vivo dosing?	No	Yes	**Yes**	Yes
Baseline antibody exclusion criteria?	No (if *ex vivo*)	Yes	**No**	No
Repeat-dose capabilities?	Yes (if *ex vivo*)	No	**Yes**	Yes
Carrying capacity?	8 kb[1]	<4 kb[1]	**>30 kb**	~12 kb[2]
Integrates payload into host cell DNA?	Yes	No	**No**	No
Regulatory precedent?	Yes	Yes	**Yes**	Yes

1. Lundstrom, K. Viral Vectors in Gene Therapy. *Diseases* 2018, 6, 42.
2. Generation Bio (GBIO) Prospectus. (2020, June 11). Retrieved September 4, 202020, https://www.sec.gov/Archives/edgar/data/1733294/000119312520167812/d924849d424b4.htm

LV = lentivirus
AAV = adeno-associated virus
LNP = lipid nanoparticle

Clinically validated platform targeting skin; broad tropism of HSV-1 could unlock additional target tissues

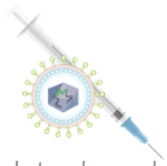
Therapeutic Vector



The current vector has been clinically validated to target skin cells. Preclinical exploration of its ability to target additional epithelial cell types is under way

Formulation / Route of Admin

Topical



Intradermal

Inhaled

Additional potential routes of administration under investigation

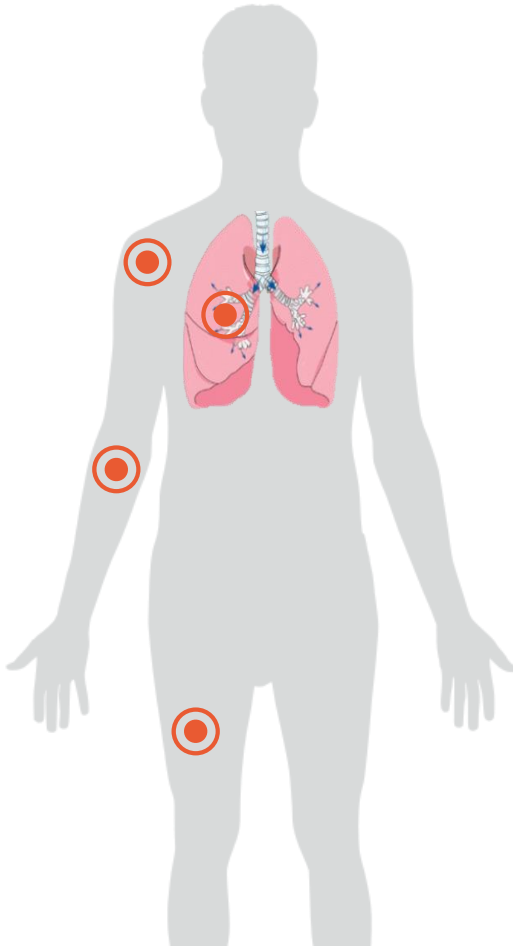
Drug Product

- ✓ B-VEC
- ✓ KB105
- • KB104
- • *Early stage research projects*

- ✓ KB301
- • KB104
- • *Early stage research projects*

- • KB407
- • *Early stage research projects*

- • *Early stage research projects*



Clinical Experience
In development
Research / Platform Development Efforts

Therapeutic pipeline

	Product	Protein	Indication	Discovery	Preclinical	Phase 1/2	Phase 3	Key Upcoming Milestone	Ownership
Dermatology	**B-VEC**†¤•Δ‡§	Type VII collagen (COL7)	Dystrophic EB					Top line Phase 3 data in 4Q21	Wholly owned
Dermatology	**KB105**†¤•‡	Transglutaminase 1 (TGM1)	TGM1-deficient ARCI					Phase 2 data and next steps in 1H21	Wholly owned
Dermatology	**KB104**¤	Serine Peptidase Inhibitor Kazal Type 5 (SPINK5)	Netherton Syndrome					File IND in 2H21	Wholly owned
Dermatology	**KB1XX**	Undisclosed programs							Wholly owned
Dermatology	**KB5XX**	Vectorized antibodies	Chronic skin conditions						Wholly owned
Respiratory	**KB407**†¤‡	Cystic fibrosis transmembrane conductance regulator (CFTR)	Cystic fibrosis					Initiate Phase 1 study in 3Q21	Wholly owned
Respiratory	**KB408**	Alpha-1 antitrypsin (AAT)	Alpha-1 antitrypsin deficiency						Wholly owned
Respiratory	**KB4XX**	Undisclosed programs							Wholly owned

All pipeline compounds are investigational, being evaluated in clinical or pre-clinical studies.

†: FDA Orphan Drug Designation;
¤: FDA Rare Pediatric Disease Designation;
•: Fast-track Designation;
Δ: FDA RMAT designation;
‡: EMA Orphan Drug Designation;
§: EMA PRIME Designation.

Aesthetics pipeline housed in wholly owned subsidiary

Program	Indication	Gene	Discovery	IND Enabling	Clinical Development	Next Milestone
KB301	Skin quality	type III collagen (COL3)	→	→	→	Phase I efficacy data in 2H21
KB302	TBA	type I collagen (COL1)	→			
KB303	TBA	elastin (ELN)	→	→		Initiate Phase I study in 2022
KB304	TBA	COL3 + ELN	→			

All pipeline compounds are investigational, being evaluated in clinical or pre-clinical studies.

†: FDA Orphan Drug Designation;
¤: FDA Rare Pediatric Disease Designation;
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Δ: FDA RMAT designation;
‡: EMA Orphan Drug Designation;
§: EMA PRIME Designation.

Platform supported by in-house manufacturing capacity and expertise

Established process conducted at Krystal's end-to-end GMP facility (Ancoris)

- Maintains control of IP/trade secrets relating to manufacturing process
- Adheres to internal process and production schedules, avoiding use of high demand gene therapy CMOs

Upstream process using stable producer cell lines has cost and regulatory benefits

- Stable complementary cell lines are developed in-house are used in established methods for production of consistent batches
- Eliminates the need for multiple cGMP qualifications of plasmids and variability in transfection efficiency from batch to batch
- Scalable from clinical phase to commercial

We have successfully developed a robust and reproducible downstream process

- Work conducted in an aseptic closed system process
- The same process is leveraged across pipeline with minimal redevelopment effort between product candidates
- Compliant with global regulatory requirements

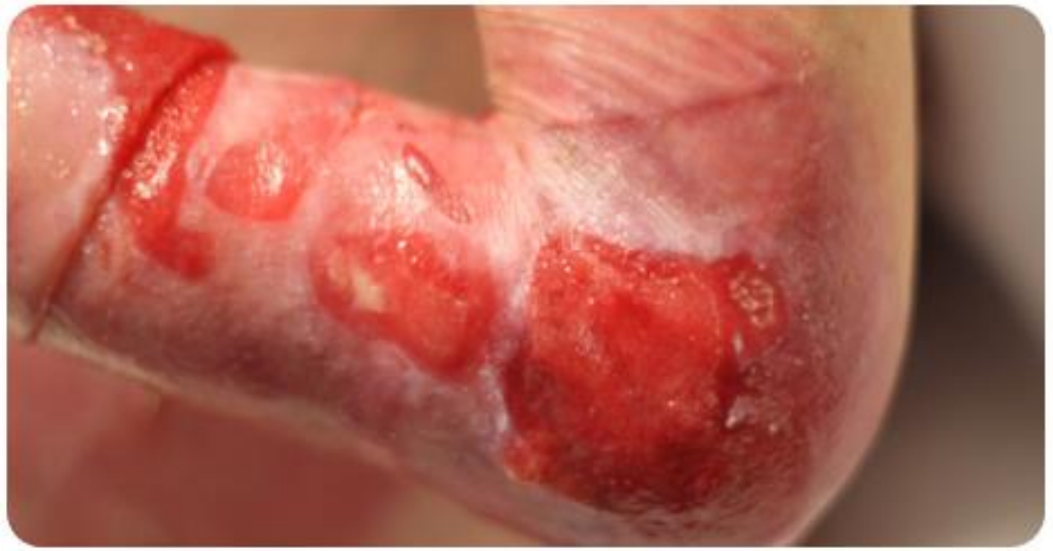
Initial focus on rare skin diseases led to rapid clinical POC and pipeline

Dystrophic epidermolysis bullosa (DEB)

"Butterfly Children" is often used to describe young DEB patients because their skin is as fragile as a butterfly's wings

Dystrophic Epidermolysis Bullosa

- A rare, genetic skin disease that causes skin to tear or blister from minor contact
- Mutations in the *COL7A1* gene lead to absent or dysfunctional COL7 protein, without which the epidermis does not anchor to the dermis
- The recessive form (RDEB) is the classic, most severe form of the condition. Dominant DEB (DDEB) has a broader range in severity and is often characterized by blistering on the hands, feet, knees, and elbows



Epidemiology

- **Prevalence**: Up to 125,000 people are affected by DEB worldwide[1]
- We believe that there are, at present, approximately 3,000 DEB patients in the US
- **Incidence:** The incidence of DEB is 6.5 per million births in the US[2]

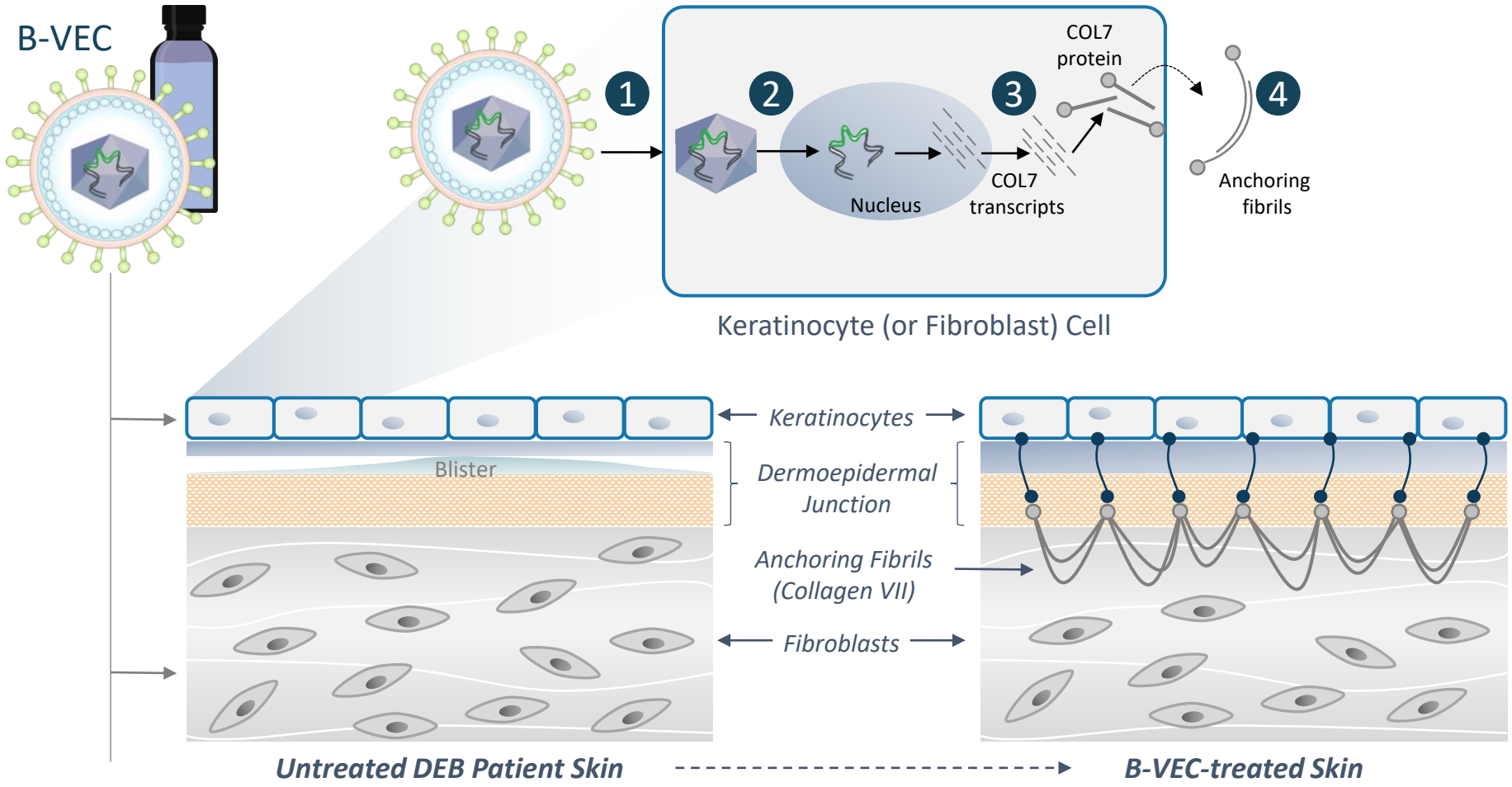
Current Standard of Care

- There are no approved treatments for DEB
- Existing therapies limited to expensive and time-consuming palliative treatments
- Palliative treatments cost $200k – $400k annually[3,4]

1. DEBRA International, http://www.debra-international.org/epidermolysis-bullosa/causes-and-subtypes.html; http://www.debra-international.org/what-is-eb/causes-and-subtypes/deb.html
2. Pfendner EG, Lucky AW. Dystrophic Epidermolysis Bullosa. 2006 Aug 21 [Updated 2015 Feb 26]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet].
3. Rashidghamat E., Mellerio J.E., Management of chronic wounds in patients with dystrophic epidermolysis bullosa: challenges and solutions, Chronic Wound Care Management and Research Volume 2017:4, 45-54
4. GENEGRAFT Report Summary. (2015, February 16). Retrieved December 13, 2016, from http://cordis.europa.eu/result/rcn/156078_en.html

Beremagene geperpavec (B-VEC) for DEB

Topically applied B-VEC gel is designed to induce local COL7 expression and molecular correction



1. B-VEC enters the compromised skin of DEB patients and transduces both keratinocytes and fibroblasts
2. Once in the nucleus of transduced cells the vector genome is deposited (episomally)
3. As a result, *COL7A1* transcripts are generated, allowing the cell to produce and secrete functional COL7 protein
4. The secreted COL7 protein assembles into anchoring fibrils which hold the epidermis and dermis together

B-VEC is an investigational therapy being studied in clinical trials

Topical B-VEC was evaluated in a Phase1/2 study

Design

- GEM1/2 (NCT03536143) was an intra-patient comparison of wounds randomized to receive either topical B-VEC or placebo.
- Each patient on-study for ~6 months; 3 months of on-site visits followed by 3-month at-home imaging period
- *Study PI: Dr. Peter Marinkovich (Stanford University)*

Enrollment

- A total of 9 RDEB patients (adult and pediatric) were enrolled in the study; 3 subjects re-enrolled later in the study and were re-randomized for a total of 12 subjects

Dosing

- In the Ph1 portion (n=2) one wound was administered B-VEC and one wound was administered placebo at a dose of 1e8 PFU/wound with varying frequency throughout the study period
- In Phase 2 portion (n=10) 2 wounds were administered B-VEC and one wound was administered placebo (except 1 patient who was 1:1) at doses of either 2e8, 3e8, 6e8 or 8e8 PFU/wound with varying frequency throughout the study period

Key Endpoints

Safety measures

- AEs, including clinically significant changes in laboratory results, vitals, and physical exam findings
- Viral shedding was analyzed through the collection of blood, urine, and skin swabs, and antibodies to HSV and COL7 were analyzed through collection of serum

Efficacy measures

- Level of collagen VII (COL7) in B-VEC-administered skin as measured by immunofluorescence; presence of anchoring fibrils as measured by immunoelectron microscopy
- Wound closure (change in wound surface area relative to baseline), time to wound closure, and duration of wound closure, all relative to placebo

B-VEC is an investigational therapy being studied in clinical trials

Repeat doses of topical B-VEC were well tolerated; COL7 expression and molecular correction established

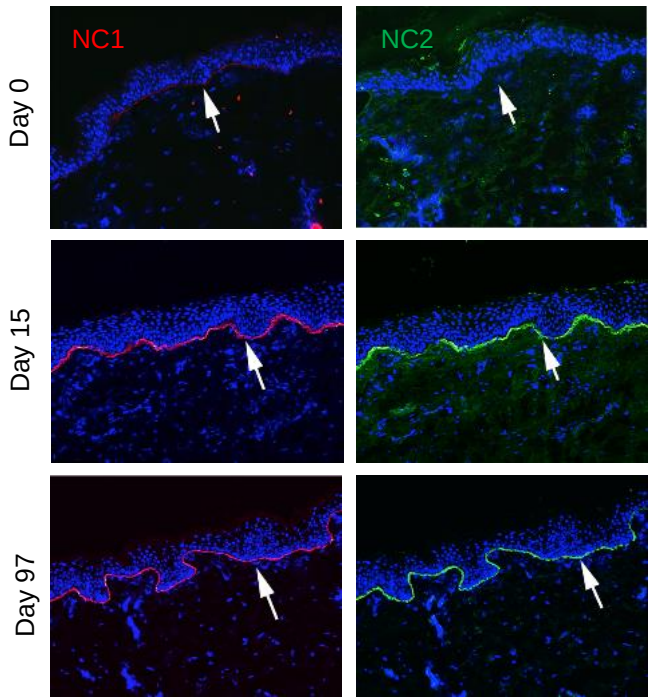
Increasing doses and dosing frequency were well tolerated

- In the Ph1/2 trial, the number of repeat doses per wound ranged from 4 to 41; the PFU per wound ranged from 1e8 to 8e8
- No treatment-related serious AEs were reported; AEs deemed possibly related were mild (n=20) or moderate (n=1)
- No immune response or blistering observed around the sites of administration following first and repeat doses
- Blood and urine samples collected throughout the study revealed:
  - No systemic viral shedding
  - No adverse events associated with routine labs (chemistry and hematology)
- Some patients had baseline COL7 and/or HSV-1 antibodies which did not impair efficacy or impact tolerance of therapy

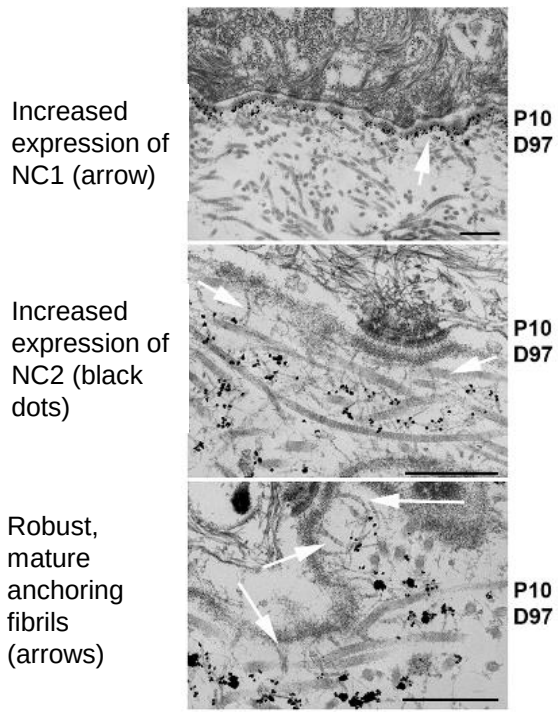
Molecular correction established and correlated with wound healing

- Expression and correct localization of full-length COL7 was observed following B-VEC therapy, evidenced by presence of *both* NC1 and NC2 domains and visible anchoring fibrils on IEM.

Baseline, Days 15 and 97 collagen VII expression using NC1 and NC2 specific antibodies (patient 10)



Immunoelectron microscopy shows mature anchoring fibrils at day 97 (patient 10)

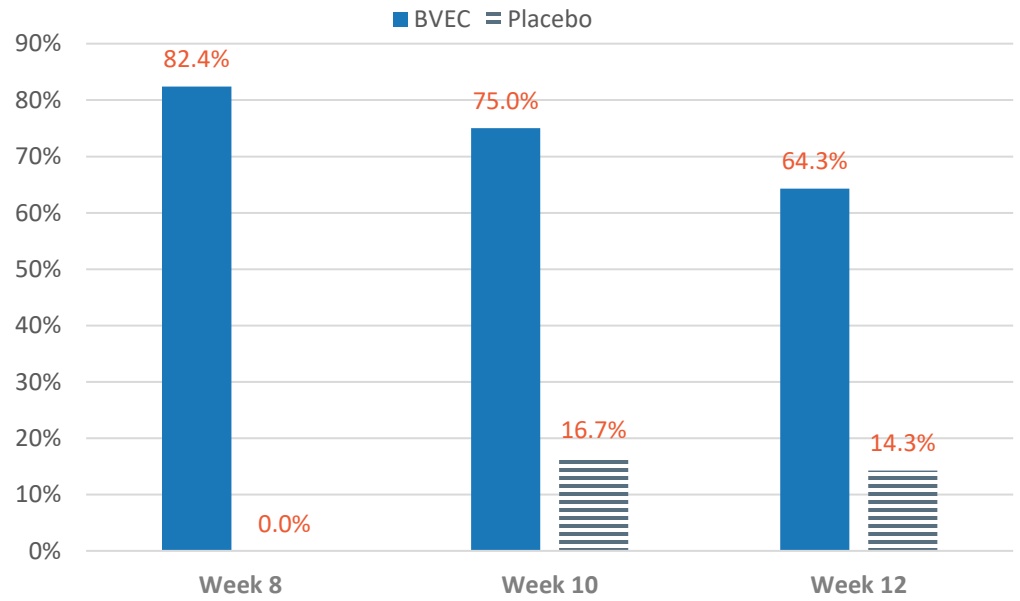


Arrows indicate basement membrane zone

B-VEC is an investigational therapy being studied in clinical trials

B-VEC showed statistically significant benefit in wound healing relative to placebo

Percentage of wounds reaching complete closure at weeks 8, 10, and 12†

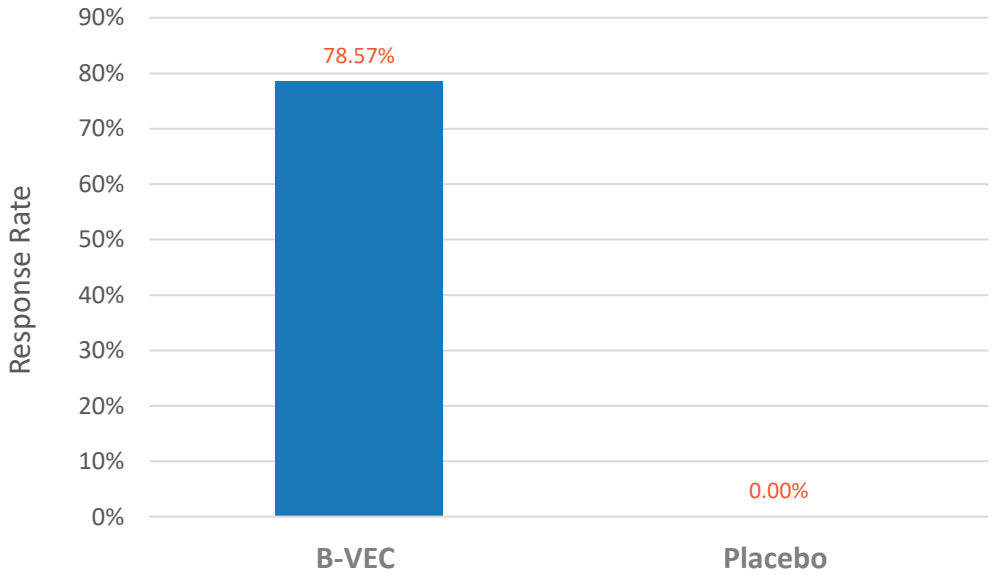


B-VEC	82.4% (14/17)	75.0% (12/16)	64.3% (9/14)
Placebo	0.0% (0/8)	16.7% (1/6)	14.3% (1/7)
p-value*	0.0001	0.0155	.0384
Combined p-value**	<0.0001		

*based on Cochran-Mantel Haenszel (CMH) Test Without Adjusting for Week-to-Week Placebo Variability
** based on the Breslow-Day for Homogeneity and Cochran-Mantel-Haenszel (CMH)Tests

†patient 12 was excluded from the analysis

78.6% of B-VEC treated wounds vs. 0% of placebo treated wounds were completely closed at weeks 8 and 10 *or* weeks 10 and 12



B-VEC	78.57% (11/14)	0.00% (0/7)
p-value*	0.00257	

*based on McNemar test

B-VEC is an investigational therapy being studied in clinical trials

The pivotal GEM-3 study is enrolling; top line data expected in 4Q21

Design

- GEM-3 (NCT04491604) is a randomized, double-blind, intra-patient comparison of wounds randomized to receive either topical B-VEC or placebo
- Each patient on-study for approximately 7 months: the 6-month dosing period followed by a 30-day safety follow up

Enrollment

- 31 DEB subjects (adult and pediatric) were enrolled in US
- Ages ranged from one (1) to forty-four (44) years old, 61% of patients were 18 years old or younger
- Each subject provided at least 1 pair (up to 3) of primary target wounds, 1 wound of the pair was randomized to B-VEC and the other to placebo
- In addition to the primary target wound pair(s), additional wounds (secondary wounds) may be selected to be treated with B-VEC in an open-label manner

Efficacy Endpoints

Primary

- Complete wound healing determined by the Investigator in B-VEC treated wounds versus placebo. A positive response is defined as:
  - Complete wound healing at Week 22 and Week 24; or
  - Complete wound healing at Week 24 and Week 26

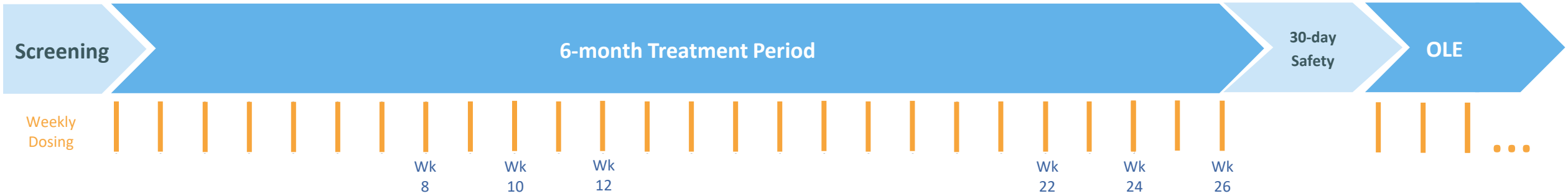
Secondary

- Complete wound healing, determined by the Investigator, as compared to baseline in B-VEC treated wounds versus placebo at weeks 8, 10 and 12
- Mean change in pain severity (using either a VAS or FLACC-R Scale) per primary wound site associated with wound dressing changes
- The proportion of primary wound sites with ≥75% would healing as compared to baseline at Week 24 using Canfield photography quantitation

B-VEC is an investigational therapy being studied in clinical trials

Phase 3 trial is well powered and inclusive of a broad patient population

*The trial is designed to maximize chances of success while maintaining potential for a broad label, inclusive of **chronic and recurring wounds of any size** in RDEB or DDEB patients*



Dosing:

- Primary wounds will be treated once weekly with a fixed dose until wound closure; should a wound re-open, weekly dosing will resume at the assigned dose until wound closure
- Each patient is allowed a maximum weekly dose of B-VEC; if that maximum is not reached in dosing primary wounds, additional secondary wounds may be chosen and treated with B-VEC in an open label manner

Key Design Elements:

- No restriction on chronic or recurring wounds
- Maximum weekly dose allows for flexibility to treat multiple and / or larger wounds
- Inclusive of RDEB *and* DDEB patients

Primary Endpoint:

- A positive response is defined as complete wound healing at weeks 22 and 24 *or* weeks 24 and 26
- The study has greater than 90% power to detect a 50% difference in response rate between B-VEC and placebo with two-sided Type 1 error rate of 5% using the McNemar test

Dose Per Wound	
Wound Area	**Dose**
<20cm^2	4x10^8 PFU
20-40cm^2	8x10^8 PFU
40-60cm^2	1.2x10^9 PFU

Maximum Weekly Dose Per Subject:	
Age	**Max Weekly Dose**
≥ 6 months to < 3 years	1.6x10^9 PFU/week
≥ 3 years to < 6 years	2.4x10^9 PFU/week
≥ 6 years	3.2x10^9 PFU/week

B-VEC is an investigational therapy being studied in clinical trials

Autosomal Recessive Congenital Icthyosis associated with TGM1 mutations

Transglutaminase-1 deficiency is associated with increased mortality in the neonatal period and has a dramatic impact on quality of life

Autosomal Recessive Congenital Ichthyosis (ARCI) Associated with TGM1

- The most common form of ARCI is caused by an inactivating mutation in the TGM1 gene encoding the enzyme transglutaminase-1, a protein that is essential for the proper formation of the skin barrier
- The condition is characterized by thick, dry, scaly skin, increased trans-epidermal water loss (TEWL), risk for dehydration, sepsis, skin malignancies, etc

Epidemiology[1-8]

- **Prevalence:** There are approximately 20,000 people affected by TGMI related icthyosis worldwide (~1,800 US; 3,000 EU; 18,000 ROW)
- **Incidence:** It is estimated that around 350-400 babies are born with the condition each year, worldwide

Current Standard of Care

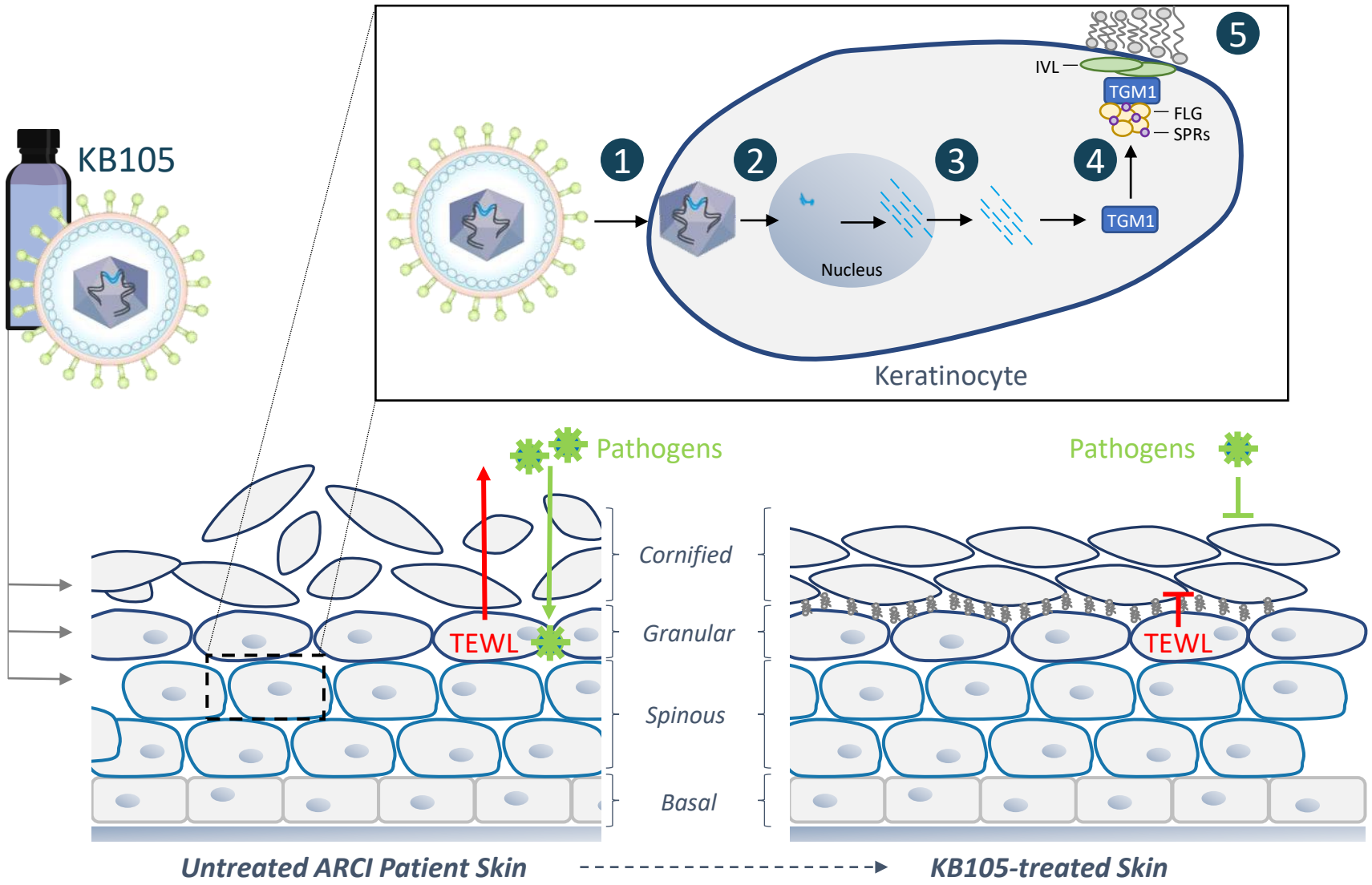
- There are no approved treatments for ARCI associated with TGM1
- Topical and systemic retinoids and time-consuming supportive treatments (up to 4 hours a day of skin care) are most often used

1. Rodriguez-Pazos et al. *Actas Dermosifiliogr.* 2013 May;104(4):270–284;
2. Dreyfus et al. *Orphanet J Rare Dis.* 2014 Jan 6;9:1;
3. Hernandez-Martin et al. *J Am Acad Dermatol.* 2012 Aug;67(2):240–244;
4. Pigg et al. *Eur J Hum Genet.* 1998 Nov-Dec;6(6):589–596.
5. Pigg et al. *Acta Derm Venereol.* 2016 Nov 2;96(7):932–937;
6. Orphanet;
7. Foundation for Ichthyosis & Related Skin Types (FIRST);
8. National Organization for Rare Disorders (NORD).

KB105 for TGM1 associated ARCI

Topically applied KB105 delivers multiple copies of the human transglutaminase 1 ("TGM1") gene

1. KB105 enters permeabilized skin and transduces keratinocytes (native TGM1-producing cells)
2. KB105 is transported into the nucleus of transduced cells and the vector genome is deposited (episomally)
3. *TGM1* transcripts are generated, which allows the cell to produce functional TGM1 protein that localizes to the cell membrane
4. TGM1 crosslinks target proteins (*e.g.*, filaggrin (FLG), involucrin (IVL), small proline-rich proteins (SPRs)) to aid in the formation of the cornified cell envelope
5. This layer, known as the stratum corneum, acts as a mechanical barrier to protect against transepidermal water loss (TEWL) and entry of infectious agents



KB105 is an investigational therapy being studied in clinical trials

KB105 is being evaluated in a Phase1/2 study

Design

- The Ph1/2 trial (NCT04047732) is an open label, intra-patient comparison of KB105 and placebo
- Each patient on-study for approximately six months; 3 months of on-site visits followed by 3-month at-home imaging period
- *Study PI: Dr. Amy Paller (Northwestern University)*

Enrollment

- ~6 TGM1-ARCI subjects will be enrolled across 2 sites; three Ph1 patients were enrolled at Paddington Testing Company (Philadelphia); Ph2 subjects will be enrolled at Northwestern (Chicago)

Dosing

- In the Ph1 portion (n=3) one or two ~20cm^2 target areas were administered placebo, and 3 target areas were administered 2x10^9 PFU with varying frequency over ~60-90 days
- In Ph1, topical and microneedle administration was evaluated; in Ph2 topical administration will be utilized

Key Endpoints

Safety measures

- AEs, including clinically significant changes in laboratory results, vitals, and physical exam findings
- Viral shedding analyzed through the collection of blood, urine, and skin swabs; antibodies to HSV and TGM1 analyzed through collection of serum

Efficacy measures

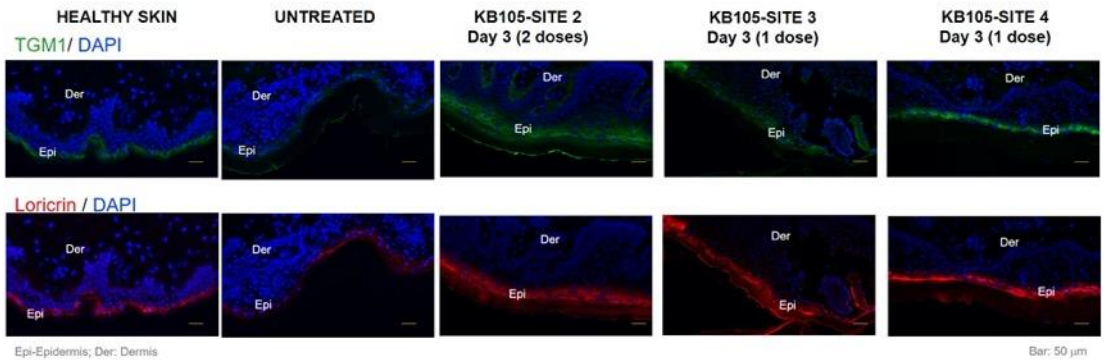
- Level of transglutaminase 1 in KB105-administered skin as measured by immunofluorescence microscopy
- Improvement of disease severity in the treatment area assessment through Investigator's Global Assessment (IGA)
- Improvement of disease severity in the treatment area through use of the Visual Index for Ichthyosis Severity scale, lamellar (VIIS-L) standard assessment

Initial data shows repeat dosing of KB105 to be well tolerated; molecular and phenotypic improvement evident

KB105 Was Well Tolerated and Generated Functional TGM1 protein

- Repeat dosing with KB105 was well tolerated with no drug related AEs and no immune response to HSV or TGM1
- No vector shedding detected in swabs, blood or urine in all three patients
- KB105 treatment restored functional TGM1 protein expression and activity in all treated sites
- KB105-expressed TGM1 was correctly localized in the epidermis, colocalizing with Loricrin, and was functionally active
- qPCR, IF, and in situ analyses demonstrated similar delivery efficacy of TGM1 DNA from single and repeat administration

Subject 1: Treatment Restored TGM1 Expression to Normal Levels

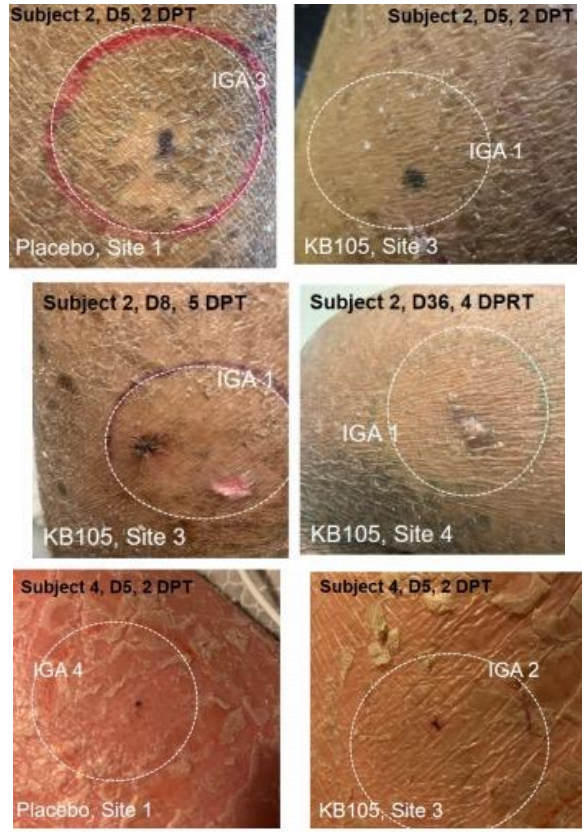


Phenotypic Improvement Evident After Topical and Microneedle Application

- Phenotypic evaluation limited by small treatment areas, but KB105 treated areas showed reduced reversion to ichthyotic scaling phenotype

DPT: Days Post Treatment

DPRT: Days Post Re-Treatment

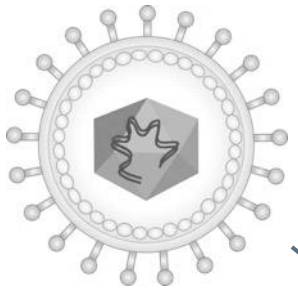


KB105 is an investigational therapy being studied in clinical trials

Leveraging platform to target new tissues and larger indications

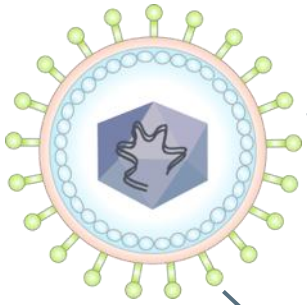
HSV-1 has potential beyond rare skin diseases

Wild-type HSV-1



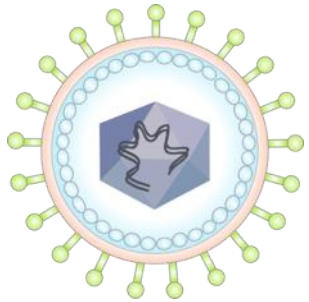
HSV-1 has natural affinity for **epithelial cells,** in addition to several other cell types, with favorable immune-evasion mechanisms

Krystal's Current Platform



- Skin
  - Rare Skin Disease
    - ✓ B-VEC (COL7A1) for DEB
    - ✓ KB105 (TGM1) for TGM1-ARCI
    - • KB104 (SPINK5) for Netherton's Disease
    - • Additional preclinical candidates
  - Aesthetics (Jeune Inc.)
    - ✓ KB301 (COL3) for Acne Scars and Wrinkles
    - • Additional preclinical candidates
  - Different Diseases
  - Different Effectors (e.g. antibodies, RNAi)
- Lung
  - Rare Lung Disease
    - • KB407 (CFTR) for Cystic Fibrosis
    - • Additional preclinical candidates
  - Different Diseases
  - Different Effectors (e.g. antibodies, RNAi)

Investing in Next Gen Technology to Maintain Leadership in HSV-1 Space



KB407 for cystic fibrosis

Gene therapy approaches have been tried and failed in their attempts to replace CFTR protein

- Viral (adenovirus and AAV) and non-viral (DNA plasmids and stabilized mRNA) approaches have been tested in more than 25 clinical trials enrolling >470 patients
- Past approaches suffer from some combination of physical limitations for large cargo, low efficiency of gene transfer, toxicity, immune intolerance, product instability, and burdensome delivery

We are developing KB407 as an inhalable, repeat dose gene therapy that delivers the full human CFTR gene

- ✓ Replication incompetent HSV-1
- ✓ Delivers two copies of full length, human CFTR protein (mutation agnostic approach)
- ✓ Duration of nebulization expected to be under 30 minutes, using a commercially available nebulizer
- ✓ Episomal delivery of CFTR gene does not disrupt cell DNA
- ✓ Ability to re-dose and/or adjust dose over time as lung cells turnover

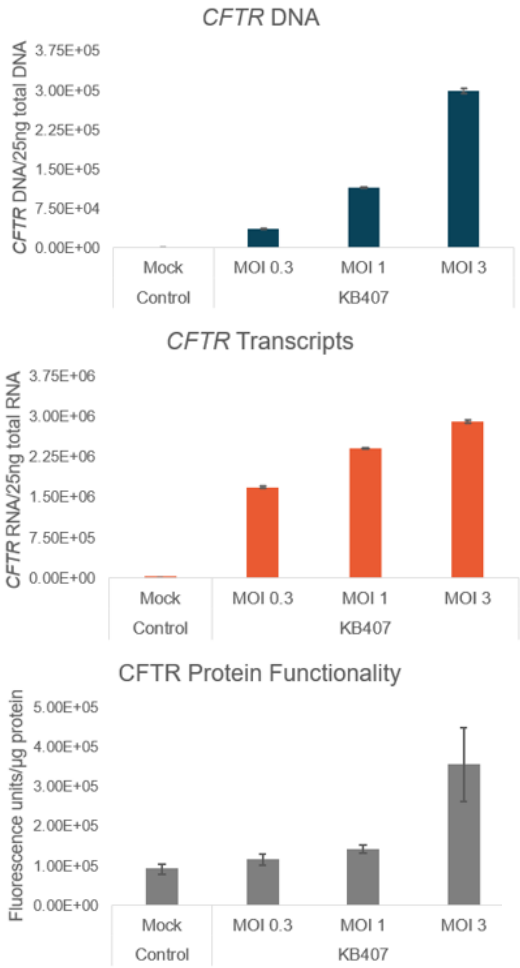
Our vector can be formulated and delivered via nebulizer with no significant change in activity

- In vitro data shows KB407 can be nebulized, successfully transduce target lung cells and induce expression of fully functional and properly localized CFTR

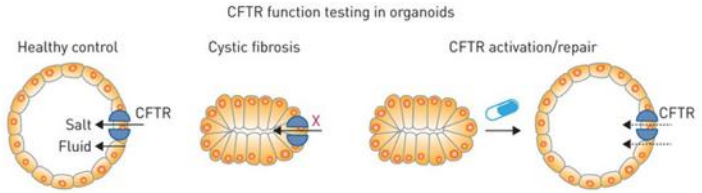
KB407 is an investigational therapy being studied in preclinical trials

Preclinical data supports KB407 in CF and broader development in lung disease

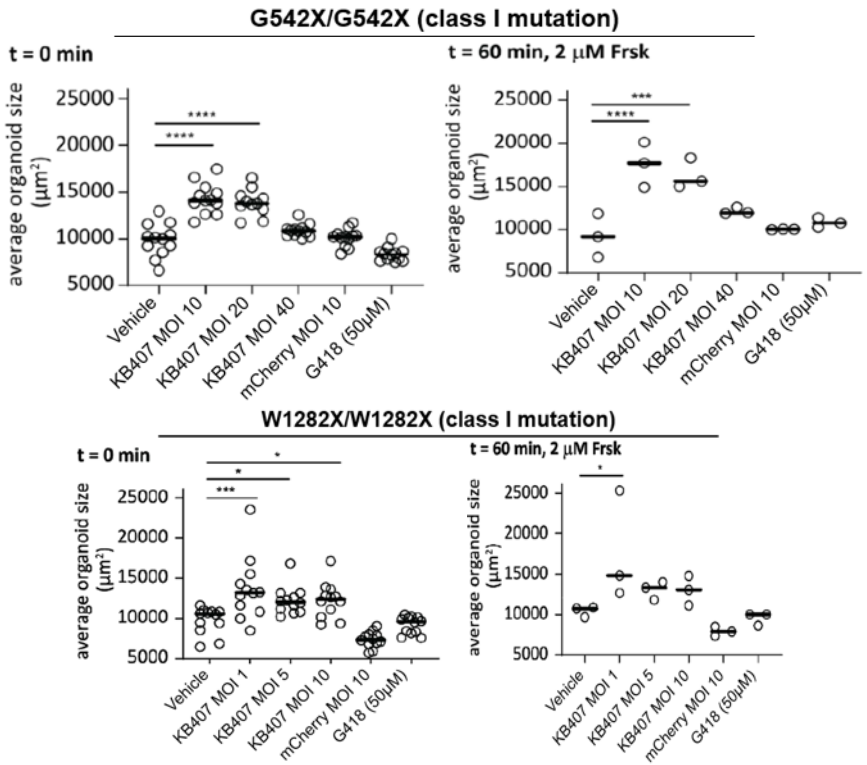
Robust, dose-dependent CFTR expression and functional correction in 2D airway epithelial cell culture



KB407-mediated functional correction of CF phenotype in clinically relevant 3D organotypic system (HUB)



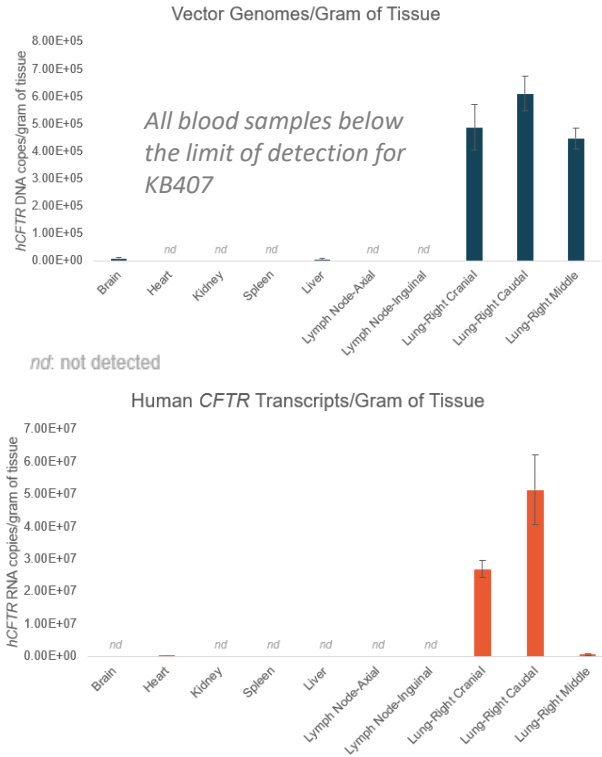
*Van Mourik *et al.* (2019). "Intestinal organoids to model cystic fibrosis".



KB407 is an investigational therapy being studied in preclinical trials

Two repeat doses of KB407 in a nonhuman primate were well tolerated and distributed broadly throughout the lung

- No abnormal cage-side/clinical observations throughout study
- No gross findings noted at time of necropsy



KB301 for aesthetic indications

KB301 and other discovery programs in Aesthetics, are housed in our wholly owned subsidiary, Jeune Inc.

KB301 aims increase neocollagenesis, thereby correcting the underlying molecular defect of the aged phenotype

- Dermal collagen, composed primarily of types 1 and 3 collagen fibrils, represents >90% (dry weight) of human skin
- Declining levels of collagen are caused by reduced collagen biosynthesis and increased collagen fibril fragmentation resulting from both intrinsic (e.g., passage of time, genetics) and extrinsic (e.g., chronic light exposure, pollution) pressures
- KB301 is designed to deliver the gene for full-length type III collagen (COL3)
- It is injected directly into the area of interest, with the goal of targeted collagen production by the body's own cells

KB301 is currently being evaluated in a Phase 1 trial (NCT04540900)

- The open label, dose ranging study will evaluate repeat dosing of KB301 injections
- Safety Endpoints
  - Safety and tolerability of KB301 based on the assessment of adverse events, physical examinations, vital signs, and clinical laboratory test results
- Efficacy Endpoints
  - Cohort 1 - COL3A1 transgene expression 2-days post-dose, as measured by qRT-PCR of skin biopsies.

Initial data from Cohort 1 of the Phase 1 study shows safety and tolerability of repeat KB301 injections

- Two repeated intradermal injections of KB301 were well tolerated and no safety signals were observed
- Recorded adverse events were transient and limited to expected mild or moderate injection site or biopsy site reactions (e.g. erythema, site pain, purpura, ecchymosis)
- No vector shedding was detected in blood, urine, or skin swabs; no meaningful changes in clinical labs were observed
- For all subjects who have completed follow up through day 90 (subjects 1-6; subject 7 follow up ongoing) no clinically significant changes in anti-drug antibodies were observed
- qRT-PCR analysis of control and KB301-treated biopsies were harvested 2-days post-dose, and show KB301-encoded COL3A1 expression at the mid and high dose, with no detectable expression in control samples
- KB301-induced COL3A1 expression was evident by day 2 following the first dose; expression levels were similar following the first and second dose, underscoring the lack of immunogenicity to the vector

KB301 is an investigational therapy being studied in preclinical trials

Financials and Milestones

Krystal summary (updated)

A fully integrated, clinical stage gene therapy company powered by proprietary HSV-1 vector technology

Current Status and Milestones

Rare Skin

- **B-VEC:** Pivotal GEM-3 trial ongoing with topline data expected 4Q21. Commercial planning in US and EU underway
- **KB105:** Phase 2 study ongoing; initial data from the first Phase 2 patient and an update on the next Phase 2 cohorts expected in 1H21
- **KB104:** Preclinical work ongoing; IND anticipated in 2H21

Aesthetics (Jeune Inc.)

- **KB301:** Phase 1 trial in aesthetic skin indications ongoing; initial Phase 1 efficacy data anticipated in 2H21

Rare Lung

- **KB407:** pre-IND work ongoing; clinical trial initiation anticipated in 3Q21

Platform

- **Manufacturing:** Ancoris facility (7,500 sqft) currently supplying all clinical material and will supply initial phase of B-VEC launch; Astra facility (150,000 sqft) construction underway, completion anticipated in 2022
- **Next Gen Tech:** Evaluation of novel effectors, routes of administration, and tissue tropism underway

December 31, 2020 cash balance of $271.3M, strengthened by $151.9 million of net proceeds from 2021 subsequent offerings

- All four rare disease programs are PRV eligible

Krystal

The Leader in Redosable Gene Therapy for Rare Disease

April 2021